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Diphenylprolinol Silyl Ether as Catalyst of an Asymmetric, Catalytic, and Direct Michael Reaction of Nitroalkanes with α,β-Unsaturated Aldehydes

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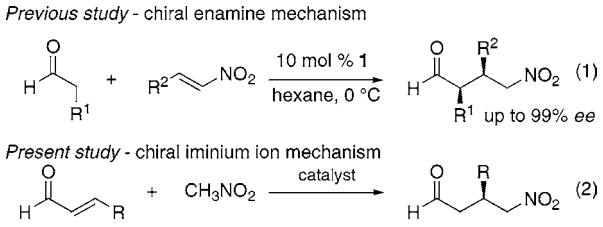
ABSTRACT

A catalytic enantioselective direct conjugate addition of nitroalkanes to α,β-unsaturated aldehydes using diphenylprolinol silyl ether as an organocatalyst has been developed. Using this methodology as a key step, short syntheses of therapeutically useful compounds have also been accomplished.

The conjugate addition of carbanions to α,β-unsaturated carbonyl compounds is one of the most fundamental carbon−carbon bond-forming reactions in organic synthesis.[1] We have reported a highly syn- and enantioselective Michael reaction catalyzed by diphenylprolinol silyl ether (**1**), in which aldehyde and nitroalkene act as Michael donor and acceptor, respectively (eq 1).[2] The Michael reaction of the reverse combination, in which nitroalkane and α,β-unsaturated aldehyde act as donor and acceptor, respectively (eq 2), is also synthetically important, as it too can provide versatile synthetic intermediates such as amino carbonyl compounds and amino alkanes. Hence, the catalytic asymmetric Michael reaction of nitroalkanes has been intensively investigated.[3] In spite of considerable effort, most of the Michael reactions of nitroalkanes that have been devised are limited to α,β-unsaturated ketones, esters, or amides. Achieving the Michael reaction of α,β-unsaturated aldehydes is thought to be difficult because the competitive 1,2-addition reaction occurs readily due to the highly reactive aldehyde.



Recently the field of organocatalysis has been developing rapidly,[4] and several organocatalysts have been successfully applied to the Michael reaction of nitroalkanes via the iminium activation strategy, although these have been limited to α,β-unsaturated ketones.[5] For α,β-unsaturated aldehydes, Maruoka and co-workers have developed an elegant chiral phase transfer Michael reaction, in which the silyl nitronates

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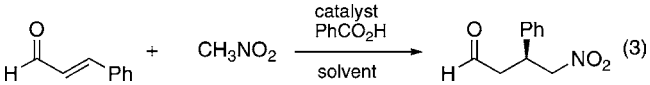
prepared from nitroethane and nitropropane were employed instead of the nitroalkanes, but they reported no results for nitromethane.[6] Arvidsson and co-workers recently reported the Michael reaction of α,β-unsaturated aldehydes with nitroalkanes catalyzed by imidazole-containing organocatalyst. The reaction had limited success with nitroethane and nitropropane, but only moderate enantioselectivity (47% ee) with nitromethane.[7] However, no widely applicable, direct Michael reactions of simple nitroalkanes, and inclusive of nitromethane, with α,β-unsaturated aldehydes have been described, in spite of the synthetic potential of such reactions.[8] In this communication, we disclose such a reaction.

The Michael reaction of nitromethane and cinnamaldehyde was selected as a model (eq 3). First silyl ethers of diarylprolinols,[9,10,11] independently developed by Jørgensen's[9] and our[2,10] groups, were used as catalyst. When diphenylprolinol silyl ether **1** was employed, the desired product was obtained with excellent enantioselectivity (98% ee), in spite of the low yield which is caused by over-reaction of the initially generated product with a second nitromethane via the Henry reaction. To improve the yield, the reaction conditions were examined in detail. It was found that both the additive and solvent used in the reaction are important. After screening of additives such as *p*-nitrophenol,[10a] $PhCO_2H$, CF_3CO_2H, $NaHCO_3$, and AcONa, the reaction was found to be accelerated in the presence of $PhCO_2H$. After screening the solvent, we found that excellent yield and enantioselectivity were achieved when MeOH[10a] was employed (Table 1). It should be noted that the bis(trifluoromethyl) substituted catalyst **2** and diphenylprolinol **3** were ineffective (entries 6, 7).

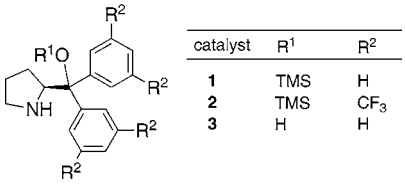


(3)

Table 1. Optimization of the Reaction Conditions[a]

entry	catalyst	solvent	time/h	yield/%[b]	ee/%[c]
1	**1**	–[d]	28	31[e]	98
2	**1**	CH_3CN	8	56	96
3	**1**	DMF	24	56	93
4	**1**	CH_2Cl_2	16	63	97
5	**1**	MeOH	16	90	95
6	**2**	MeOH	16	57	82
7	**3**	MeOH	16	52	77

[a] Unless otherwise shown, the reaction was performed employing cinnamaldehyde (0.6 mmol), nitromethane (1.8 mmol), catalyst (0.06 mmol), $PhCO_2H$ (0.12 mmol), and solvent (1.2 mL) at rt. [b] Isolated yield. [c] Optical purity was determined by the chiral GC analysis. [d] Neat reaction conditions without $PhCO_2H$. [e] 1,5-Dinitro-4-phenyl-1-pentene was obtained in 22% yield.



catalyst	R^1	R^2
1	TMS	H
2	TMS	CF_3
3	H	H

Figure 1. Organocatalysts examined in this study.

As the best conditions had been found, the generality of the reaction was investigated, with the results summarized in Table 2. Not only phenyl, but also a 2-naphthyl-substituted acrolein derivative gave an excellent result (entry 2). The reaction proceeds efficiently for acrolein derivatives not only with electron-rich aromatic substituents such as 3,4-methylenedioxyphenyl and *p*-methoxyphenyl (entries 3, 4), but also with electron-deficient substituents such as *p*-bromophenyl, *p*-chlorophenyl, and *p*-nitrophenyl (entries 5−8),

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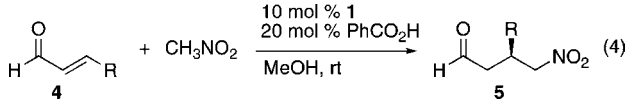
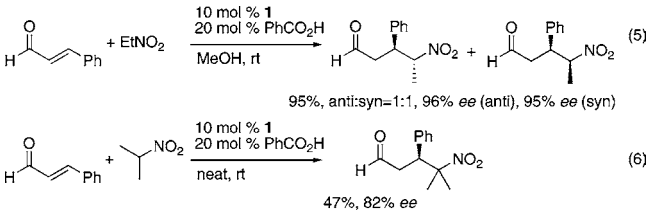
Table 2. Catalytic Asymmetric Michael Reaction of CH_3NO_2 and α,β-Unsaturated Aldehydes[a]



entry	R	time/h	yield/%[b]	ee/%[c]
1	Ph **4a**	16	90	95
2	2-naph **4b**	16	94	93
3	3,4-methylenedioxyphenyl **4c**	17	80	93
4	*p*-MeOPh **4d**	16	88	95
5	*p*-BrPh **4e**	17	87	95
6	*p*-ClPh **4f**	17	83	94
7[d]	*p*-ClPh **4f**	40	80	92
8[e]	*p*-NO_2Ph **4g**	48	76	95
9	2-furyl **4h**	24	82	93
10	*n*-Bu **4i**	42	53	90
11[f]	*n*-Bu **4i**	96	77	91
12[f]	*i*-Bu **4j**	120	68	91
13[f]	$PhCH_2CH_2$ **4k**	96	76	92

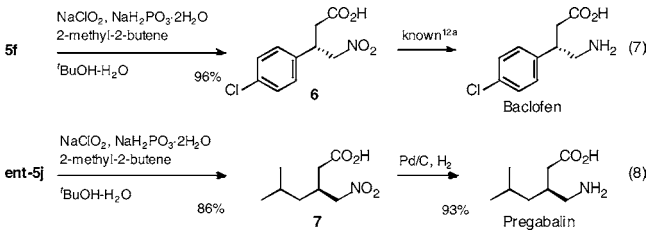
[a] Unless otherwise shown, the reaction was performed employing α,β-unsaturated aldehyde (0.6 mmol), nitromethane (1.8 mmol), **1** (0.06 mmol), $PhCO_2H$ (0.12 mmol) and MeOH (1.2 mL) at rt. [b] Isolated yield. [c] Optical purity was determined by chiral GC or HPLC analysis, see Supporting Information for details. [d] Catalyst loading is 2 mol %. [e] The reaction was performed at 4 °C. [f] The reaction was performed without $PhCO_2H$.

to afford excellent enantioselectivities in all the cases examined. Heteroaromatic groups such as furyl are suitable substituents (entry 9). In the case of alkyl group-substituted acrolein, good yield and excellent enantioselectivities were obtained without addition of $PhCO_2H$ (entries 11−13). The loading of the catalyst can be reduced to 2 mol % (entry 7).



Not only nitromethane but also other nitroalkanes can be used successfully. Nitroethane reacts with cinnamaldehyde in MeOH to afford the adduct in 95% yield with excellent enantioselectivity, while the diastereoselectivity was 1:1 (eq 5). Though the reactivity of a β,β-disubstituted nitroalkane was low, 2-nitropropane reacts with cinnamaldehyde under neat conditions to afford the Michael adduct in moderate yield with high enantioselectivity (eq 6).

Because of the synthetic versatility of the nitro and aldehyde groups, short syntheses of a broad range of chiral pharmaceuticals would be possible by employing the present Michael reaction as a key step. Baclofen[5c,12] is a therapeutically useful $GABA_B$ receptor agonist, which was synthesized in only two steps, an oxidation and a reduction (eq 7), from **5f**, prepared by the current Michael reaction using 2 mol % of the catalyst (Table 2, entry 7). Pregabalin,[3c,12c,13] an important anticonvulsant drug, was also synthesized via a similar two-step sequence from **ent-5j**, which had been prepared using **ent-1** (eq 8).



In summary, we have developed a catalytic, enantioselective, direct conjugate addition of nitroalkanes to α,β-unsaturated aldehydes using diphenylprolinol silyl ether as an organocatalyst. This reaction expands the previous substrate scope significantly and is the successful reaction using nitromethane directly with α,β-unsaturated aldehydes. Using this methodology as a key step, short syntheses of therapeutically useful compounds can be realized. It is interesting to note that the same catalyst **1** is effective in the enantioselective Michael reaction of both the α,β-unsaturated aldehyde/nitroalkane and the inverse nitroalkene/aldehyde substrate pairs.

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Supporting Information Available: Detailed experimental procedures, full characterization, copies of ^{1}H- and ^{13}C NMR and IR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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